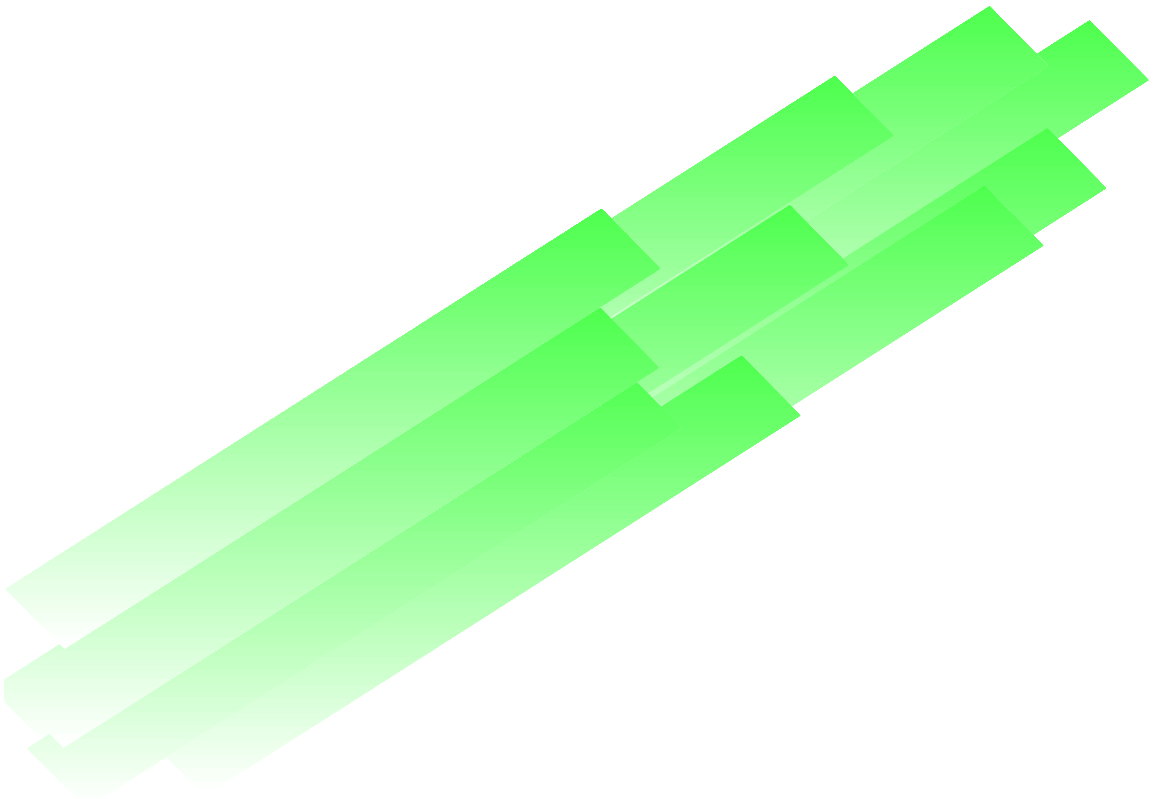
Guidance for Industry

Labeling Guidance for Zolpidem Tartrate Tablets



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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GUIDANCE FOR INDUSTRY[1]

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I. INTRODUCTION

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (Ambien®; Lorex Pharmaceuticals; 19-908/S-002; Approved July 14, 1995; Revised April 11, 1994). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

II. LABELING

CIV

[Include unless excepted status has been obtained from DEA.]

ZOLPIDEM TARTRATE TABLETS

DESCRIPTION

Zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class. Chemically, zolpidem is *N*,*N*,6-Trimethyl-2-*p*-tolylimidazo(1,2-α)pyridine-3-acetamide L-(+)-tartrate (2:1). Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88 and the molecular formula $(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$. It has the following structural formula:

[INSERT STRUCTURAL FORMULA HERE]

Each tablet for oral administration, contains __ mg zolpidem tartrate. In addition, each tablet contains the following inactive ingredients: *[Please note that in accordance with good*

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[1]This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance).]

CLINICAL PHARMACOLOGY

Pharmacodynamics: Subunit modulation of the $GABA_A$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the $GABA_A$ receptor complex is located on its alpha (α) subunit and is referred to as the benzodiazepine (BZ) or omega (ω) receptor. At least three subtypes of the omega receptor have been identified.

While zolpidem is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties, it interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which nonselectively bind to and activate all three omega receptor subtypes, zolpidem *in vitro* binds the (ω_1) receptor preferentially. The (ω_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the (ω_1) receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

Pharmacokinetics: The pharmacokinetic profile of zolpidem tartrate is characterized by rapid absorption from the GI tract and a short elimination half-life ($T_{1/2}$) in healthy subjects. In a reported single-dose crossover study in 45 healthy subjects administered 5 mg and 10 mg zolpidem tartrate tablets, the mean peak concentrations (C_{max}) were 59 (range: 29 to 113) and 121 (range: 58 to 272) ng/mL, respectively, occurring at a mean time (T_{max}) of 1.6 hours for both. The mean zolpidem elimination half-life was 2.6 (range: 1.4 to 4.5) and 2.5 (range: 1.4 to 3.8) hours, for the 5 mg and 10 mg tablets, respectively. Zolpidem tartrate is converted to inactive metabolites that are eliminated primarily by renal excretion. Zolpidem demonstrated linear kinetics in the dose range of 5 mg to 20 mg. Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/mL. Zolpidem did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate tablets for 2 weeks.

In a reported food-effect study in 30 healthy male volunteers compared the pharmacokinetics of zolpidem tartrate tablets 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 15% and 25%, respectively, while mean T_{max} was prolonged by 60% (from 1.4 to 2.2 hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, zolpidem tartrate tablets should not be administered with or immediately after a meal.

In the elderly, the dose for zolpidem tartrate tablets should be 5 mg (see PRECAUTIONS and

DOSAGE AND ADMINISTRATION). This recommendation is based on several studies in which the mean C_{max}, $T_{1/2}$, and AUC were significantly increased when compared to results in young adults. In one study of eight elderly subjects (>70 years), the means for C_{max}, $T_{1/2}$, and AUC significantly increased by 50% (255 vs 384 ng/mL), 32% (2.2 vs 2.9 hr), and 64% (955 vs 1,562 ng·hr/mL), respectively, as compared to younger adults (20 to 40 years) following a single 20 mg oral zolpidem dose. Zolpidem did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

The pharmacokinetics of zolpidem in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20 mg oral zolpidem dose, mean C_{max} and AUC were found to be two times (250 vs 499 ng/mL) and five times (788 vs 4,203 ng·hr/mL) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normals of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

The pharmacokinetics of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean $Cl_{Cr} = 6.5 \pm 1.5$ mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max}, half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. On day 1, C_{max} was 172 ± 29 ng/mL (range: 46 to 344 ng/mL). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/mL (range: 28 to 316 ng/mL). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5 to 3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5 to 2.0 hr). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On day 1, $T_{1/2}$ was 2.4 ± 0.4 hr (range 0.4 to 5.1 hr). After repeated dosing, $T_{1/2}$ was 2.5 ± 0.4 hr (range: 0.7 to 4.2 hr). AUC was 796 ± 159 ng·hr/mL after the first dose and 818 ± 170 ng·hr/mL after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function. As a general precaution, these patients should be closely monitored.

Postulated Relationship Between Elimination Rate of Hypnotics and Their Profile of Common Untoward Effects: The type and duration of hypnotic effects and the profile of unwanted effects during administration of hypnotic drugs may be influenced by the biologic half-life of administered drug and any active metabolites formed. When half-lives are long, drug or metabolites may accumulate during periods of nightly administration and be associated with impairment of cognitive and/or motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be enhanced. In contrast, if half-lives, including half-lives of active metabolites, are short, drug and metabolites will be cleared before the next dose is ingested, and carryover effects related to excessive sedation or CNS depression should be minimal or absent. Zolpidem has a short half-life and no active metabolites. During nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of

hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of other rapidly eliminated hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety. Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with zolpidem.

Controlled Trials Supporting Safety and Efficacy

TRANSIENT INSOMNIA: Normal adults experiencing transient insomnia (n=462) during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing two doses of zolpidem (7.5 mg and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings.

CHRONIC INSOMNIA: Adult outpatients with chronic insomnia (n=75) were evaluated in a double-blind, parallel group, 5 week trial comparing two doses of zolpidem tartrate (10 mg and 15 mg) and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 15 mg was superior to placebo for all 5 weeks; zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

Adult outpatients (n=141) with chronic insomnia were evaluated in a double-blind, parallel group, 4 week trial comparing two doses of zolpidem (10 mg and 15 mg) and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first treatment week. Zolpidem 15 mg was superior to placebo on a subjective measure of sleep latency for the first 3 weeks, on a subjective measure of total sleep time for the first week, and on number of awakenings and sleep quality for the first 2 weeks.

NEXT-DAY RESIDUAL EFFECTS: There was no evidence of residual next-day effects seen with zolpidem in several studies utilizing the Multiple Sleep Latency Test (MSLT), the Digit Symbol Substitution Test (DSST), and patient ratings of alertness. In one study involving elderly patients, there was a small but statistically significant decrease in one measure of performance, the DSST, but no impairment was seen in the MSLT in this study.

REBOUND EFFECTS: There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of zolpidem. There was subjective evidence of impaired sleep in the elderly on the first posttreatment night at doses above the recommended elderly dose of 5 mg.

MEMORY IMPAIRMENT: Two small studies (n=6 and n=9) utilizing objective measures of memory yielded little evidence for memory impairment following the administration of zolpidem tartrate. There was subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of zolpidem, predominantly at doses above 10 mg.

EFFECTS ON SLEEP STAGES: In studies that measured the percentage of sleep time spent in each sleep stage, zolpidem has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

INDICATIONS AND USAGE

Zolpidem tartrate tablets are indicated for the short-term treatment of insomnia. Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks.

Zolpidem tartrate tablets should not be prescribed in quantities exceeding a 1 month supply (see WARNINGS).

Zolpidem tartrate has been shown to decrease sleep latency and increase the duration of sleep for up to 5 weeks in controlled clinical studies (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

None known.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness which should be evaluated. Worsening

of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including zolpidem. Because some of the important adverse effects of zolpidem appear to be dose related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the smallest possible effective dose, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS depressant drugs (see DRUG ABUSE AND DEPENDENCE).

Zolpidem, like other sedative/hypnotic drugs, has CNS depressant effects. Due to the rapid onset of action, zolpidem should only be ingested immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of zolpidem. Zolpidem showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS depressant drugs. Dosage adjustments may be necessary when zolpidem is administered with such agents because of the potentially additive effects.

PRECAUTIONS

General

USE IN THE ELDERLY AND/OR DEBILITATED PATIENTS: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended zolpidem tartrate dosage is 5 mg in such patients (see DOSAGE AND ADMINISTRATION) to decrease the possibility of side effects. These patients should be closely monitored.

USE IN PATIENTS WITH CONCOMITANT ILLNESS: Clinical experience with zolpidem in patients with concomitant systemic illness is limited. Caution is advisable in using zolpidem in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although studies did not reveal respiratory depressant effects at hypnotic doses of zolpidem in normals or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), precautions should be observed if zolpidem tartrate is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received. Data in end-stage renal failure patients repeatedly treated with zolpidem did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored (see CLINICAL PHARMACOLOGY - Pharmacokinetics). A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored.

USE IN DEPRESSION: As with other sedative/hypnotic drugs, zolpidem should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information for Patients: Patient information is printed at the end of this insert. To assure safe and effective use of zolpidem, this information and instructions provided in the patient information section should be discussed with patients.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions

CNS ACTIVE DRUGS: Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance.

The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated.

Since the systematic evaluations of zolpidem tartrate in combination with other CNS active drugs have been limited, careful consideration should be given to the pharmacology of any CNS active drug to be used with zolpidem. Any drug with CNS depressant effects could potentially enhance the CNS depressant effects of zolpidem.

OTHER DRUGS: A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil; however, no significant alterations in zolpidem pharmacokinetics were found.

Drug/laboratory Test Interactions: Zolpidem is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

CARCINOGENESIS: Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10 mg human dose on a mg/kg or mg/m^2 basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10 mg human dose on a mg/kg or mg/m^2 basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.

MUTAGENESIS: Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice.

IMPAIRMENT OF FERTILITY: In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4 mg to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m^2. No effects on any other fertility parameters were noted.

Pregnancy

TERATOGENIC EFFECTS: Pregnancy Category B. Studies to assess the effects of zolpidem on

human reproduction and development have not been conducted.

Teratology studies were conducted in rats and rabbits.

In rats, adverse maternal and fetal effects occurred at 20 mg and 100 mg base/kg and included dose-related maternal lethargy and ataxia and a dose-related trend to incomplete ossification of fetal skull bones. Underossification of various fetal bones indicates a delay in maturation and is often seen in rats treated with sedative/hypnotic drugs. There were no teratogenic effects after zolpidem administration. The no-effect dose for maternal or fetal toxicity was 4 mg base/kg or 5 times the maximum human dose on a mg/m^2 basis.

In rabbits, dose-related maternal sedation and decreased weight gain occurred at all doses tested. At the high dose, 16 mg base/kg, there was an increase in postimplantation fetal loss and underossification of sternebrae in viable fetuses. These fetal findings in rabbits are often secondary to reductions in maternal weight gain. There were no frank teratogenic effects. The no-effect dose for fetal toxicity was 4 mg base/kg or 7 times the maximum human dose on a mg/m^2 basis.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NONTERATOGENIC EFFECTS: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

Labor and Delivery: Zolpidem has no established use in labor and delivery.

Nursing Mothers: Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal volunteers (2.6 ± 0.3 hr). Between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown.

In addition, in a rat study, zolpidem inhibited the secretion of milk. The no-effect dose was 4 mg base/kg or 6 times the recommended human dose in mg/m^2.

The use of zolpidem in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment: Approximately 4% of 1,701 patients who

received zolpidem at all doses (1.25 mg to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 6% of 1,320 patients who received zolpidem at all doses (5 mg to 50 mg) in similar foreign trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.6%), amnesia (0.6%), dizziness (0.6%), headache (0.6%), and nausea (0.6%).

Incidence in Controlled Clinical Trials

MOST COMMONLY OBSERVED ADVERSE EVENTS IN CONTROLLED TRIALS: During short-term treatment (up to 10 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (28 to 35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

Adverse Events Observed at an Incidence of ≥ 1% in Controlled Trials: The following tables enumerate treatment emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received zolpidem tartrate in U.S. placebo-controlled trials. Events reported by investigators were classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

The following table was derived from a pool of 11 placebo-controlled short-term U.S. efficacy trials involving zolpidem in doses ranging from 1.25 mg to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

Incidence of Treatment-Emergent Adverse Experiences in Short-term Placebo-Controlled Clinical Trials (Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤ 10 mg) (N=685)	Placebo (N=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Nausea	2	3
Diarrhea	1	-
Musculoskeletal System		
Myalgia	1	2

*Events reported by at least 1% of zolpidem patients are included.

The following table was derived from a pool of three placebo-controlled long-term efficacy trials involving zolpidem tartrate. These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem at doses of 5 mg, 10 mg, or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse events occurring at an incidence of at least 1% for zolpidem patients.

Incidence of Treatment-Emergent Adverse Experiences in Long-term Placebo-Controlled Clinical Trials (Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (≤ 10 mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	-
Chest pain	1	-
Fatigue	1	2

Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Headache	19	22
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	-
Amnesia	1	-
Anxiety	1	1
Nervousness	1	3
Sleep disorder	1	-
Gastrointestinal System		
Nausea	6	6
Dyspepsia	5	6
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1
Immunologic System		
Infection	1	1
Musculoskeletal System		
Myalgia	7	7
Arthralgia	4	4
Respiratory System		
Upper respiratory infection	5	6
Sinusitis	4	2
Pharyngitis	3	1
Rhinitis	1	3
Skin and Appendages		
Rash	2	1
Urogenital System		
Urinary tract infection	2	2

* Events reported by at least 1% of patients treated with zolpidem.

DOSE RELATIONSHIP FOR ADVERSE EVENTS: There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Adverse Event Incidence Across the Entire Preapproval Database: Zolpidem was administered to 3,021 subjects in clinical trials throughout the U.S., Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms. The frequencies presented, therefore, represent the proportions of the 3,021 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with zolpidem, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

AUTONOMIC NERVOUS SYSTEM: Infrequent: increased sweating, pallor, postural hypotension. Rare: altered saliva, flushing, glaucoma, hypotension, impotence, syncope, tenesmus.

BODY AS A WHOLE: Infrequent: asthenia, edema, falling, fever, malaise, trauma. Rare: allergic reaction, allergy aggravated, abdominal body sensation, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

CARDIOVASCULAR SYSTEM: Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM: Frequent: ataxia, confusion, euphoria, insomnia, vertigo. Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, migraine, paresthesia, sleeping (after daytime dosing), stupor, tremor. Rare: abnormal thinking, aggressive reaction, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypotonia, hysteria, illusion, intoxicated feeling, leg cramps, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

GASTROINTESTINAL SYSTEM: Infrequent: constipation, dysphagia, flatulence, gastroenteritis, hiccup. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

HEMATOLOGIC AND LYMPHATIC SYSTEM: Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura.

IMMUNOLOGIC SYSTEM: Rare: abscess, herpes simplex, herpes zoster, otitis externa, otitis media.

LIVER AND BILIARY SYSTEM: Infrequent: increased SGPT. Rare: abnormal hepatic function, bilirubinemia, increased SGOT.

METABOLIC AND NUTRITIONAL: Infrequent: hyperglycemia. Rare: gout, hypercholesteremia, hyperlipidemia, increased BUN, periorbital edema, thirst, weight decrease.

MUSCULOSKELETAL SYSTEM: Infrequent: arthritis. Rare: arthrosis, muscle weakness, sciatica, tendinitis.

REPRODUCTIVE SYSTEM: Infrequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast neoplasm, breast pain.

RESPIRATORY SYSTEM: Infrequent: bronchitis, coughing, dyspnea. Rare: bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia.

SKIN AND APPENDAGES: Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

SPECIAL SENSES: Frequent: diplopia, vision abnormal. Infrequent: eye irritation, scleritis, taste perversion, tinnitus. Rare: corneal ulceration, eye pain, lacrimation abnormal, photopsia.

UROGENITAL SYSTEM: Infrequent: cystitis, urinary incontinence. Rare: acute renal failure, dysuria, micturition frequency, polyuria, pyelonephritis, renal pain, urinary retention.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Zolpidem tartrate is classified as a Schedule IV controlled substance by federal regulation.

Abuse and Dependence: Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The U.S. clinical trial experience from zolpidem does not reveal any clear evidence for withdrawal syndrome. Nevertheless, the following adverse events included in

DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, light-headedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence, during treatment at recommended doses.

Because individuals with a history of addiction to, or abuse of, drugs or alcohol are at risk of habituation and dependence, they should be under careful surveillance when receiving zolpidem or any other hypnotic.

OVERDOSAGE

Signs and Symptoms: In European postmarketing reports of overdose with zolpidem alone, impairment of consciousness has ranged from somnolence to light coma. There was one case each of cardiovascular and respiratory compromise. Individuals have fully recovered from zolpidem tartrate overdoses up to 400 mg (40 times the maximum recommended dose). Overdose cases involving multiple CNS depressant agents, including zolpidem, have resulted in more severe symptomatology, including fatal outcomes.

Recommended Treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdosage, even if excitation occurs. The value of dialysis in the treatment of overdosage has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

Poison Control Center: As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdosage.

DOSAGE AND ADMINISTRATION

The dose of zolpidem tartrate tablets should be individualized.

The recommended dose for adults is 10 mg immediately before bedtime.

Downward dosage adjustment may be necessary when zolpidem is administered with agents having known CNS-depressant effects because of the potentially additive effects.

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Patients with hepatic insufficiency do not clear the drug as rapidly as normals. An initial 5 mg dose is recommended in these patients (see PRECAUTIONS).

The total zolpidem tartrate dose should not exceed 10 mg.

HOW SUPPLIED

- Established Name
- Strength of dosage form
- Packaging, NDC number
- Dosage form, shape, color, scoring, imprinting
  Note: The innovator's tablets are unscored.
- Store below 30°C (86°F).
- "Dispense in" statement.
- "Caution: Federal Law..." statement.

Include the following information at the end of the insert:

- Date of latest revision.
- "Manufactured by" statement. - Should be consistent with container labels and/or carton labeling.
- Ensure the full text of the patient package insert is reprinted at the end of the physician insert.

INFORMATION FOR PATIENTS TAKING ZOLPIDEM TARTRATE TABLETS

Your doctor has prescribed zolpidem tartrate tablets to help you sleep. The following information is intended to guide you in the safe use of this medicine. It is not meant to take the place of your doctor's instructions. If you have any questions about zolpidem be sure to ask your doctor or pharmacist.

Zolpidem is used to treat different types of sleep problems, such as:

- trouble falling asleep
- waking up too early in the morning
- waking up often during the night

Some people may have more than one of these problems.

Zolpidem belongs to a group of medicines known as the "sedative/hypnotics," or simply, sleep medicines. There are many different sleep medicines available to help people sleep better. Sleep problems are usually temporary, requiring treatment for only a short time, usually 1 or 2 days up to 1 or 2 weeks. Some people have chronic sleep problems that may require more prolonged use of sleep medicine. However, you should not use these medicines for long periods without talking with your doctor about the risks and benefits of prolonged use.

SIDE EFFECTS

Most Common Side Effects: All medicines have side effects. Most common side effects of sleep medicines include:

- drowsiness
- dizziness
- lightheadedness
- difficulty with coordination

You may find that these medicines make you sleepy during the day. How drowsy you feel depends upon how your body reacts to the medicine, which sleep medicine you are taking, and how large a dose your doctor has prescribed. Daytime drowsiness is best avoided by taking the lowest dose possible that will still help you sleep at night. Your doctor will work with you to find the dose of zolpidem that is best for you.

To manage these side effects while you are taking this medicine:

- When you first start taking zolpidem or any other sleep medicine until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while doing anything that requires complete alertness, such as driving a car, operating machinery, or piloting an aircraft.

- NEVER drink alcohol while you are being treated with zolpidem or any sleep medicine. Alcohol can increase the side effects of zolpidem or any other sleep medicine.

• Do not take any other medicines without asking your doctor first. This includes medicines you can buy without a prescription. Some medicines can cause drowsiness and are best avoided while taking zolpidem tartrate tablets.

• Always take the exact dose of zolpidem prescribed by your doctor. Never change your dose without talking to your doctor first.

SPECIAL CONCERNS

There are some special problems that may occur while taking sleep medicines.

Memory Problems: Sleep medicines may cause a special type of memory loss or "amnesia." When this occurs, a person may not remember what has happened for several hours after taking the medicine. This is usually not a problem since most people fall asleep after taking the medicine.

Memory loss can be a problem, however, when sleep medicines are taken while traveling, such as during an airplane flight and the person wakes up before the effect of the medicine is gone. This has been called "traveler's amnesia."

Memory problems are not common while taking zolpidem. In most instances memory problems can be avoided if you take zolpidem only when you are able to get a full night's sleep (7 to 8 hours) before you need to be active again. Be sure to talk to your doctor if you think you are having memory problems.

Tolerance: When sleep medicines are used every night for more than a few weeks, they may lose their effectiveness to help you sleep. This is known as "tolerance." Sleep medicines should, in most cases, be used only for short periods of time, such as 1 or 2 days and generally no longer than 1 or 2 weeks. If your sleep problems continue, consult your doctor, who will determine whether other measures are needed to overcome your sleep problems.

Dependence: Sleep medicines can cause dependence, especially when these medicines are used regularly for longer than a few weeks or at high doses. Some people develop a need to continue taking their medicines. This is known as dependence or "addiction."

When people develop dependence, they may have difficulty stopping the sleep medicine. If the medicine is suddenly stopped, the body is not able to function normally and unpleasant symptoms (see Withdrawal) may occur. They may find they have to keep taking the medicine either at the prescribed dose or at increasing doses just to avoid withdrawal symptoms.

All people taking sleep medicines have some risk of becoming dependent on the medicine. However, people who have been dependent on alcohol or other drugs in the past may have a higher chance of becoming addicted to sleep medicines. This possibility must be considered before using these medicines for more than a few weeks.

If you have been addicted to alcohol or drugs in the past, it is important to tell your doctor before starting zolpidem or any sleep medicine.

Withdrawal: Withdrawal symptoms may occur when sleep medicines are stopped suddenly after being used daily for a long time. In some cases, these symptoms can occur even if the medicine has been used for only a week or two.

In mild cases, withdrawal symptoms may include unpleasant feelings. In more severe cases, abdominal and muscle cramps, vomiting, sweating, shakiness, and rarely, seizures may occur. These more severe withdrawal symptoms are very uncommon.

Another problem that may occur when sleep medicines are stopped is known as "rebound insomnia." This means that a person may have more trouble sleeping the first few nights after the medicine is stopped than before starting the medicine. If you should experience rebound insomnia, do not get discouraged. This problem usually goes away on its own after 1 or 2 nights.

If you have been taking zolpidem or any other sleep medicine for more than 1 or 2 weeks, do not stop taking it on your own. Always follow your doctor's directions.

Changes in Behavior and Thinking: Some people using sleep medicines have experienced unusual changes in their thinking and/or behavior. These effects are not common. However, they have included:

- more outgoing or aggressive behavior than normal
- loss of personal identity
- confusion
- strange behavior
- agitation
- hallucinations
- worsening of depression
- suicidal thoughts

How often these effects occur depends on several factors, such as a person's general health, the use of other medicines, and which sleep medicine is being used. Clinical experience with zolpidem suggests that it is uncommonly associated with these behavior changes.

It is also important to realize that it is rarely clear whether these behavior changes are caused by the medicine, an illness, or occur on their own. In fact, sleep problems that do not improve may be due to illnesses that were present before the medicine was used. If you or your family notice any changes in your behavior, or if you have any unusual or disturbing thoughts, call your doctor immediately.

Pregnancy: Sleep medicines may cause sedation of the unborn baby when used during the last weeks of pregnancy.

Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking zolpidem tartrate tablets.

SAFE USE OF SLEEPING MEDICINES

To ensure the safe and effective use of zolpidem or any other sleep medicine, you should observe the following cautions:

1. Zolpidem is a prescription medicine and should be used ONLY as directed by your doctor. Follow your doctor's instructions about how to take, when to take, and how long to take zolpidem tartrate tablets.

2. Never use zolpidem or any other sleep medicine for longer than directed by your doctor.

3. If you notice any unusual and/or disturbing thoughts or behavior during treatment with zolpidem tartrate or any other sleep medicine, contact your doctor.

4. Tell your doctor about any medicines you may be taking, including medicines you may buy without a prescription. You should also tell your doctor if you drink alcohol. DO NOT use alcohol while taking zolpidem or any other sleep medicine.

5. Do not take zolpidem or any other sleep medicine unless you are able to get a full night's sleep before you must be active again. For example, zolpidem or any other sleep medicine should not be taken on an overnight airplane flight of less than 7 to 8 hours since "traveler's amnesia" may occur.

6. Do not increase the prescribed dose of zolpidem or any other sleep medicine unless instructed by your doctor.

7. When you first start taking zolpidem or any other sleep medicine until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while doing anything that requires complete alertness, such as driving a car, operating machinery, or piloting an aircraft.

8. Be aware that you may have more sleeping problems the first night or two after stopping zolpidem or any other sleep medicine.

9. Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking zolpidem.

10. As with all prescription medicines, never share zolpidem or any other sleep medicine with anyone else. Always store zolpidem or any other sleep medicine in the original container out of reach of children.

11. Zolpidem works very quickly. You should only take zolpidem tartrate tablets right before going to bed and are ready to go to sleep.

- "Manufactured by" statement. - Should be consistent with container labels and/or carton labeling.
- Include Revision Date.

CONTAINER LABEL

In addition to the general label requirements ("Caution: Federal Law..." statement, statement of net quantity, etc.) please include the following:

Main Panel:

- The established name and strength should read as follows:

  ZOLPIDEM TARTRATE TABLETS

  __ mg

- If manufacturing multiple strengths, we encourage you to differentiate your product strengths by boxing, contrasting colors or some other means.

- This drug product is classified as a schedule IV controlled substance. See regulations regarding the placement and size of the symbol on container labels and/or carton and insert labeling.

Side Panel:

- Store below 30°C (86°F).
- "Dispense in" statement.

- "Usual Dosage" statement should read as follows:

  Usual Dosage: One tablet at bedtime. See insert.